Veterinary Dermatology
Dermatologie vétérinaire

Pemphigus foliaceous

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Introduction

The epidermis consists of multiple layers of keratinocytes and makes up the outer layers of the skin (1). The keratinocytes in the epidermis are held together by desmosomes, which are cell-cell adhesion molecules made of several different proteins, such as desmocolin and desmoglein (1). These adhesion molecules are frequent targets for autoimmune diseases and their destruction results in superficial blistering or acantholysis (1). Pemphigus foliaceous is the most common autoimmune disease in dogs and is most often caused by autoantibodies targeting desmocollin-1 (2,3).

Clinical presentation

The classical lesions of pemphigus foliaceous are large pustules that span multiple hair follicles (1,4). The pustules often begin as papules and rapidly progress to crusts and erosions (1,4). Lesions occur most commonly on the trunk, inner pinnae, face, and footpads and are generally symmetrical (4,5). Mucosal lesions are extremely rare and are not considered a feature of pemphigus foliaceous (4). Pruritus is common and dogs with severe generalized disease can have anorexia, depression, fever, and weight loss (1,3,4).

Several breeds are reported as predisposed, but the Akita and chow chow are consistently reported as being overrepresented (3). Other breeds that have been reported as overrepresented include cocker spaniel, dachshund, doberman, collie, and Shar-pei (3). Secondary bacterial infections are common and can make the diagnosis more challenging (1,4). Involvement of the pinnae, nasal planum, and paw pads is more suggestive of pemphigus foliaceous than bacterial pyoderma which more commonly affects the ventrum (1).

Most cases of pemphigus foliaceous are idiopathic, but drug-induced cases have been reported, although the evidence is often weak (1,3,4). A history of atopic dermatitis and flea allergy dermatitis is common, but since these are often found in the general canine population it is unclear if there is truly an increased incidence (5,6). Disease progression can vary widely with some patients showing a rapid progression and other cases having a more gradual course (1,4).

Diagnostics

Cytology is a useful tool when initially examining a dog suspected to be suffering from pemphigus foliaceous. It is important to rule out bacterial pyoderma, which is the main

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differential diagnosis for pemphigus foliaceous (1). Cytology from cases of pemphigus foliaceous classically shows acantholytic keratinocytes associated with intact neutrophils and occasional eosinophils (1,4). Intracellular and extracellular bacteria may be seen if there is a secondary bacterial infection (4). Acantholytic keratinocytes are rounded, darkly staining nucleated keratinocytes with features of normally differentiated spinous or granular layer epithelial cells (1,3). Unfortunately, they are not seen exclusively with pemphigus foliaceous, as they have also been reported in cases of dermatophytosis and bacterial pyoderma so these must be ruled out (1).

A definitive diagnosis should be obtained using histopathology before instituting treatment. Dogs with secondary bacterial pyoderma should be treated with antibiotics for 2 to 4 wk before obtaining biopsies whenever possible. Biopsies should be taken from intact pustules or tightly adherent crusts. Care should be taken to avoid rupturing the pustules or removing the crusts while obtaining samples. This typically means that the skin should not be scrubbed. If a crust falls off the sample, it should be included in the formalin jar. Multiple punch or wedge biopsy samples should be taken and submitted to a dermatohistopathologist.

The classical histopathological findings for pemphigus foliaceous are subcorneal pustules containing rafts of acantholytic keratinocytes (7). These pustules are often layered and span multiple hair follicles (7). Nondegenerate neutrophils, and less commonly eosinophils, are typically present within the pustules (4,7). Special stains to rule out dermatophytosis should be considered (7).

Routine hematology and biochemistry should be performed before instituting therapy for pemphigus foliaceous (1). A severe neutrophilia is common (1).

Treatment

Treatment of pemphigus foliaceous requires the use of immunosuppressive medications. Corticosteroids are the most commonly used medications either as a single agent or concurrently with a second immunosuppressive medication (1,4). Prednisone or prednisolone at a dose of 2 mg/kg body weight (BW) per day either given once daily or divided into twice daily dosing is the most common medication used (3). Some clinicians prefer to use methylprednisolone because it has less mineralocorticoid activity and may cause less polyuria and polydipsia (8). Refractory cases may respond to more potent glucocorticoids such as triamcinolone (0.2 to 0.6 mg/kg BW per day) or dexamethasone (0.2 to 0.4 mg/kg BW per day) (8). Short- and long-term side effects are common with corticosteroid usage and include polyuria, polydipsia, polyphagia, panting, increased risk of infections (urinary tract infections, pyoderma, demodicosis, dermatophytosis), alopecia, cutaneous atrophy, calcinosis cutis, and steroid hepatopathy (1,8,9).

One retrospective study did not find a significant difference in treatment outcomes for cases treated with corticosteroid monotherapy compared with prednisone and azathioprine used in combination (4). Regardless of these findings, many clinicians (including the author) typically begin with a combination of a corticosteroid and a second immunosuppressive medication for cases of generalized pemphigus foliaceous and reserve single agent corticosteroids for mild cases (1).

If there is secondary bacterial infection it should be treated. Antibiotic use at the beginning of treatment was associated with a better outcome in 1 study, but other studies have not found a significant difference between cases treated with and without antibiotics (4,6).

Azathioprine is the most frequently reported secondary immunosuppressive medication used to treat pemphigus foliaceous (1,4). Azathioprine is a purine antagonist that is less expensive than many of the other immunosuppressive medications (1). Side effects include pancreatitis, bone marrow suppression, and hepatotoxicity, so a baseline complete blood cell count and serum biochemistry profile should be obtained prior to initiating therapy (1,10). This should be repeated after 2 wk, 4 wk, and monthly for the first 3 mo (10). Hepatotoxicity is most likely to occur within the first 2 to 4 wk and bone marrow suppression typically occurs with prolonged usage (10). It is typically dosed at 2.2 mg/kg BW once daily and clinical response can take 3 to 6 wk (1,9).

Cyclosporine has been reported to have variable success in managing pemphigus foliaceous (11–13). Cyclosporine is a calcineurin inhibitor that is commonly used to treat atopic dermatitis in dogs (1,13). Transient vomiting and diarrhea are the most common side effects and the maximal effect is typically seen after 4 wk (9,13). Anecdotally, freezing the capsules and administering them frozen reduces the incidence of vomiting and does not appear to impact the bioavailability (13,14). The use of the brand name microemulsified product is preferred, but this medication is unfortunately very expensive and can be cost-prohibitive in large dogs. Doses between 5 to 10 mg/kg BW per day are typically recommended for pemphigus foliaceous (8,13).

Mycophenolate mofetil is a purine antagonist that has not been used as extensively as azathioprine, but is gaining popularity in the treatment of pemphigus foliaceous (1,15). Mycophenolate mofetil has fewer side effects than azathioprine, so intensive monitoring of blood is not required (1,9). Diarrhea is the most common side effect reported and clinical response can take 3 to 8 wk (1,9,15). Doses of 20 to 40 mg/kg BW per day divided into 2 to 3 doses daily are recommended for pemphigus foliaceous (9,15).

Typically treatment with corticosteroids, with or without a secondary immunosuppressive agent, is instituted and continued until complete remission is achieved (1). The corticosteroids are then tapered by 25% every 2 to 4 wk until doses less than 0.5 mg/kg BW every other day for prednisone, 0.05 to 0.1 mg/kg BW every 2 to 3 d for dexamethasone, or 0.1 to 0.2 mg/kg BW every 2 to 3 d for triamcinolone are achieved (1). The secondary agent is then tapered with the ultimate goal of giving the corticosteroid and secondary agent every other day on alternating days (1,8).

For milder cases, the use of a combination of tetracycline (or doxycycline) and niacinamide has been reported (16). This combination of an antibiotic and a B vitamin has immunomodulatory effects, although the exact mechanisms are not fully understood (1). Hepatotoxicity has been rarely reported with doxycycline, and generally this combination is well-tolerated (9).

This drug combination has a very slow onset of action, which limits its utility in cases of pemphigus foliaceous that are generalized or severely pruritic (1). This can be combined with corticosteroids to try to hasten the onset of action (8). Tetracycline and niacinamide are dosed at 500 mg of each 3 times daily for dogs weighing > 10 kg and 250 mg of each 3 times daily for dogs weighing < 10 kg (8,16). Topical glucocorticoids or tacrolimus 0.1% could also be considered for localized lesions (1,8).

Prognosis

Retrospective studies have found variable treatment success rates, but generally most cases have a positive response to treatment (1,3). An older retrospective study reported a 1-year survival of 53% and another had a case fatality rate of 60.5% (5,6). Newer retrospective studies have had more positive outcomes with 52% of cases achieving complete remission, 35% partial remission, and only 13% euthanized in 1 study (4). The most common reasons for euthanasia were treatment failure, treatment side effects, and poor quality of life (6). Survival beyond 10 mo is associated with a positive long-term outcome (6). There does not appear to be any difference in treatment outcomes for dogs with localized *versus* generalized disease or rapid onset *versus* slow onset (4). Most patients with pemphigus foliaceous will require lifelong treatment with medication although they are tapered to the lowest effective dose (1). A few patients may have prolonged periods of remission after their treatments have been withdrawn (4,17).

In conclusion, pemphigus foliaceous is the most common autoimmune disease affecting dogs (1). It is most commonly associated with bilaterally symmetrical crusting affecting the head, trunk, and footpads (4,5). A definitive diagnosis is made with histopathology, but cytology should be used to help differentiate cases from superficial pyodermas (1,4). Treatment typically requires immunosuppressive doses of glucocorticoids with or without a secondary immunosuppressive medication (1,4,5,8). Many clinicians initiate treatment with a combination of glucocorticoids and a secondary immunosuppressive medication but there is no clear evidence that this improves outcomes over glucocorticoid monotherapy (4). Most patients will require lifelong treatment, but the doses should be tapered to the lowest effective dose (1). A few patients may be euthanized due to treatment failure, treatment side effects, or poor quality of life, which most commonly occurs during the early phase of treatment (6).

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